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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/030,061	02/25/1998	MATTHEW TODD GILLSPIE	GILLISPIE-1	6893

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EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/030,061	GILLSPIE ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION

Applicant's amendment in paper No. 16, filed on 24 June 2002 is acknowledged and entered. Following the amendment, claims 1-6, and 8-28 are canceled, and the new claims 29-32 are added.

Currently, claims 29-32 are pending and under consideration.

The finality of the rejection of the last Office Action (paper No. 15) is withdrawn in view of new grounds of rejection.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 1-6, 8-10, and 28 are moot as the applicant has canceled the claims.

Formal Matters:

Claim 29 is objected to for using (I) and (ii) as they should be kept consistent.

Double Patenting Rejections:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 29-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, and 4 of U.S. Patent No. 6,207,641 B1, in view of U.S. Patent No. 4,588,585, U.S. Patent No. 5,776,731, or U.S. Patent No. 6,156,301.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claim 29 of the instant application is directed to a therapeutic composition comprising SEQ ID NO:6 and/or variant thereof. SEQ ID NO:6 of the instant case is 100% identical to SEQ ID NO:1 of U.S. patent 6,207,641, and the protein of SEQ ID NO:6 and the variants (recited as "a functional equivalent of said IL-18") are used as an effective ingredient in an osteoclastgenic inhibitory composition, wherein functional equivalents have one or more Cys replaced, and optionally one amino acid residue replaced, or one amino acid residue added or removed in SEQ ID NO:6. Claim 1 of the U.S. patent '641 is directed to a pharmaceutical composition comprising human IL-18 (SEQ ID NO:1), or homologous polypeptide thereof as an effective ingredient, wherein the homologous polypeptides has one amino acid residue replaced, or one amino acid residue added or deleted from the N- or C-terminus of SEQ ID NO:1. Said homologous of SEQ ID NO:1, therefore, includes the variant species in claim 29, of the present application, which are derived from SEQ ID NO:6, and have one amino acid (cysteine) replaced. Additionally, SEQ ID NO:1 of the human IL-18 in '641 contains sequences of SEQ ID NOs:1, 2, and 4 recited in claim 29 of the present application. Therefore, the pharmaceutical composition in claim 1 of the US patent includes the osteoclastgenic inhibitory composition in claim 29 of the instant case as both have the same effective ingredient. Although the current claim 29 recites a specific intended use for the composition, the composition of the '641 patent would be consistent with that use. The limitations of claims 30 and 31 of the present application are directed to a physical form of the composition (claim 30), and stabilizers (claim 31), which are indicated in the limitations of claims 3 and 4 of the U.S. patent. Claim 3 of patent '641 teaches a pharmaceutical composition of claim 1, further comprising at least one member selected from the group consisting of stabilizers, adjuvants, excipients, diluents, and biologically-active substances, indicating the composition is in a possible form of a liquid, paste, or solid, and claim 4 of patent '641 further

teaches wherein the stabilizer is selected from the group consisting of serum albumin, gelatin, maltose, and trehalose. Serum albumin, and maltose or trehalose are proteins, and saccharides, respectively. With respect to claim 32, the limitation is "wherein said warm-blooded animal is human", which does not alter the nature of the composition. Therefore, such limitation does not change the scope of the claimed composition. Thus, the conflicting claims are not patentably distinct from each other.

The primary reference does not specifically teach the amino acid replacement of cysteine of human IL-18.

However, Mark et al in patent '585 teaches that biologically active proteins may contain cysteine residues that are nonessential to their activity but are free to form undesirable intermolecular or intramolecular links (column 1, lines 22-26), and that it would be desirable to alter the proteins in a manner that does not affect their activity adversely but reduces or eliminates their ability to form intermolecular or intramolecular links that cause the protein to adopt an undesirable tertiary structure (column 1, lines 41-50). The reference further teaches a synthetic mutein of a biologically active protein which has at least one of such cysteine residues deleted or replaced by another amino acid (column 2, lines 13-18, and claim 2), and a method for making said synthetic mutein (column 2, lines 38-56).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a mutein of human IL-18 with one or more cysteine residues replaced, based on the amino acid sequence taught by Torigoe in patent '641 using the method taught by Mark because of the desirable advantage suggested by Mark. The person of ordinary skill in the art would have been motivated to do so because of the therapeutic value of the IL-18 as taught by Torigoe, and reasonably would have expected success because Mark has exemplified as regards such muteins of IFN-β and IL-2, and indicated that the teachings apply to any other biologically active protein that contains a functionally nonessential cysteine (column 3, lines 49-54).

Applicants argument to this regard, filed on 24 June 2002 (paper No. 16) has been fully considered, but is not deemed persuasive for reasons below.

At page 5 of the response, the applicant argues that Mark merely teaches the Cys residue in IFN-β and IL-2 is not indispensable for the biological activity of these cytokines, and provides no information about other cytokines, such IL-18, and that applicants believe that it is quite difficult to understand that the findings of Mark can be extrapolated to IL-18. This argument is not persuasive because the art, in general, acknowledges that some of cysteine residues in many proteins can be substituted or deleted to avoid undesirable intermolecular or intramolecular structures, and provides ample evidence in doing so. For example, Parnet et al. in '731 teaches 2F1 (IL-18R) polypeptide variants, in which cysteine residues that are not essential for biological activity are deleted or replaced with other amino acids, and indicates that such cysteine deletion or substitution prevents formation of incorrect intramolecular disulfide bridges upon renaturation (column 6, lines 47-50). Furthermore, as another example of cytokines, Namen et al. in patent '301 teaches biologically active homologues including muteins in which one or more cysteine residues have been deleted or replaced (column 13, lines 47-49, and claims 1-4). Therefore, cysteine substitution is a conventional practice, and as the present invention merely claims the IL-18 having any one or more Cys residues replaced without specified position, it is rendered obvious by the prior art.

Finally, in *Ex parte Mark* (12 USPQ2d 1904), it is clearly said that:

> "claims, for cysteine-depleted muteins of biologically active proteins, which require mutein which is produced to retain biological activity of native protein, are enabling, in view of record establishing that, for given protein having cysteine residues, one skilled in art would be able to routinely determine whether deletion or replacement of cysteine residues would result in mutein which is within claims, and fact that given protein may not be amenable for use in present invention, in that cysteine residues are needed for biological activity of protein, does not militate against conclusion of enablement, since one skilled in art is clearly enabled to perform such work as needed to determine whether cysteine residues of any given protein are needed for retention of biological activity".

The instant invention is directed to a composition comprising an IL-18 variant, which has one or more cysteine residues replaced, and is similar to the situation in *Ex parte Mark*, which indicates that it is a routine in the art to make functional variants with deletion or replacement of cysteine residues for a given protein with known function.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-32 are also rejected under 35 U.S.C. 103(a) as being obvious over claims 1, 3, and 4 of U.S. Patent No. 6,207,641 B1, in view of U.S. Patent No. 4,588,585, U.S. Patent No. 5,776,731, or U.S. Patent No. 6,156,301, for the same reasons addressed above.

The applied reference, '641, has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 29-32 are further provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 33, 37, and 38 of copending Application No. 08/982,285, which has an earlier effective filing date, and has been

allowed. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 29, 33, 37, and 38 in the copending application are directed to an artificial polypeptide derived from a wild-type human IL-18 polypeptide having SEQ ID NO:4, wherein one or more cysteine residues are replaced (claims 29 and 33); and a pharmaceutical composition thereof (claims 37 and 38). SEQ ID NO:6 of the instant case is 100% identical to SEQ ID NO:4 of the copending Application '285, and claims 29-32 of the instant application are directed to a therapeutic composition comprising SEQ ID NO:6 and/or variant thereof ("a functional equivalent of said IL-18"), wherein "said functional equivalent" comprises the amino acid sequence of SEQ ID NO:6 with one or more cysteine residues replaced. Although the form of the composition is not mentioned in the claims in '285, claim 37 teaches a physiologically acceptable carrier, indicating that the composition is in a possible form of a liquid, paste, or solid. As so, and for the reasons set forth above, the conflicting claims are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been issued as a patent.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA § 102(e)).

Claims 29-32 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 08/982,285, which has a common inventor and assignee with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application, and is for the same reasons addressed above.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is indefinite because as the claim is directed to a composition of IL-18 with SEQ ID NO:6 and/or a variant thereof, it is unclear what is SEQ ID NO:7 as recited at in the last line of the claim. The claim is further indefinite for reciting "optionally". It is unclear whether any of the limitations which follow the term "optionally" are required limitations. Therefore, the metes and bounds of the claim are unclear.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ushio et al., EP 0 712 931 A2, or Okamura et al., US 5,912,324 and further in view of Mark et al., US 4,588,585, for the reasons of record applied to claim 28 in the last Office Action, paper No. 15, mailed on 27 March 2002, at pages 5-6.

Applicants argument in paper No. 16, at page 5 has been fully considered, but is not deemed persuasive for reasons addressed above.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

DJ
7/16/02